REMARKS

Claims 1 and 5-35 were pending. Claims 12-35, withdrawn from consideration, have been cancelled without prejudice. The Office rejected claims 1 and 5-11. Applicants have herein amended claims 1, 5 and 7.

New claims 36-47 have been added and fall within elected Group I (as set forth in the Restriction Requirement mailed March 18, 2002). Support for the amendments and new claims can be found, *inter alia*, at page 2, lines 18-21; page 6, lines 7-15 and 23-27; page 11, lines 23-27; page 14, lines 10-15; page 19, lines 16-20; page 22, lines 19-24; and page 23, lines 3-7 of the specification.

No new matter has been added.

Upon entry of this paper, claims 1, 5-11 and 36-47 will be pending.

Request for Continued Examination (RCE)

Applicants attach hereto a Request for Continued Examination. Applicants specifically request that the amendments provided in Applicants' February 17, 2006 Response ***not*** be entered. Nonetheless, Applicants include in the present "Amendment and Response" amendments identical to those previously submitted but unentered, as well as further amendments to the claim set. Applicants further include herein a full and complete response to the November 17, 2005 Office Action.

Withdrawal of Rejections

35 U.S.C. §112, first paragraph

In the Advisory Action mailed May 11, 2006 ("Advisory Action"), the Office indicated that the rejections under 35 U.S.C. §112, first paragraph (written description and enablement), "would drop" if the amendment to claim 1 set forth in Applicants' Reply filed 17 February 2006 was entered. Applicants have herein amended claim 1 consistent with the amendment set forth in Applicants' 17 February 2006 Reply. Accordingly, Applicants respectfully request confirmation that claim 1 is allowable.

Double Patenting

Applicants acknowledge the Office's indication that the provisional rejection of claims 1 and 5-11 under 35 U.S.C §101 (as allegedly "claiming the same invention as that of claims 1-11 of copending Application No. 10/200,026 (filed July 18, 2002) ..."), has been rendered moot in view of "the cancellation of claims 1-11" in Ser. No. 10/200,026. (*See* Advisory Action mailed). Applicants note that Application Ser. No. 10/200,026 issued as U.S. Patent 7,081,517.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1 and 5-11 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Because one of skill in the art would readily understand that Applicants were in possession of the claimed invention at the time of filing, Applicants respectfully disagree.

Preliminarily, Applicants note that as discussed above in relation to "Withdrawal of Rejections", claim 1, as amended, is free of the rejection under 35 U.S.C. §112, first paragraph (written description and enablement). Claims 6-11, which depend directly or indirectly from claim 1, should also be allowable.

Applicants further note that the claims have been amended to refine the description of the claimed genus. For example, claim 5 has been amended to recite that the isolated nucleic acid molecule comprises a polynucleotide encodes a polypeptide having an amino acid sequence of SEQ ID NO:2 with "no more than 5 conservative amino acid substitutions". Claim 5 was also amended to recite that the encoded polypeptides are expressed at a higher level in metastatic cells relative to non-metastatic cells.

New claim 36 recites polynucleotides that are at least 95% identical to polynucleotides encoding SEQ ID NO:2, or full complements thereof, and recite that the encoded polypeptides are expressed at a higher level in metastatic cells relative to non-metastatic cells. New claim 39 recites polynucleotides encoding polypeptides that are at least 95% identical to SEQ ID NO:2

and recite that the encoded polypeptides are expressed at a higher level in metastatic cells relative to non-metastatic cells. New dependent claims recite that the polynucleotides are at least 98% identical to polynucleotides encoding SEQ ID NO:2 or that the polynucleotides encode polypeptides at least 98% identical to SEQ ID NO:2. New claims 43-47 recite further structural information regarding the encoded polypeptides. The polynucleotides recited in new claims 36-47 specifically share a function in that they all encode a polypeptide expressed at a higher level in metastatic cells relative to non-metastatic cells.

Application of the analysis set forth in Example 14 of the Written Description Guidelines demonstrates that the written description requirement is satisfied for these claims. To illustrate, the following paragraphs closely track the text of Example 14.

First, the present specification exemplifies a protein, hsOAF, having homology to the known Drosophila protein. A nucleotide sequence of hsOAF is set forth in SEQ ID NO:1, and an amino acid sequence of hsOAF is set forth in SEQ ID NO:2. A signal peptide of hsOAF is set forth as SEQ ID NO:3 and a predicted protease cleavage site is identified between amino acids at positions 25 and 26 of SEQ ID NO:3. The specification contemplates homologs of the polynucleotides that encode hsOAF wherein the homologs can have a recited percent identity (see, e.g., page 18, lines 16-20). The specification also contemplates variants (e.g., functionally equivalent polypeptides) of hsOAF wherein the variant can have any or all of the following: recited percent identity (see, e.g., page 11, lines 23-26); and substitutions (see, e.g., page 14, lines 10-15). The specification discusses potential substitutions of SEQ ID NO:2 (see, e.g., page 12, line 3, to page 14, line 15). The procedures for making variants of SEQ ID NO:2 are conventional in the art, and assays are described which will identify variants of SEQ ID NO:2 that are likely to be phenotypically silent. The application indicates that variants of SEQ ID NO:2 include but are not limited to those variants of SEQ ID NO:2 with substitution, deletion, or addition of one or more amino acids; but all variants must be expressed at higher levels in metastatic cells relative to non-metastatic cells and must at least 95% identical to SEQ ID NO:2 or contain SEQ ID NO:2 with no more than 5 amino acid substitutions, such as conservative substitutions.

SEQ ID NO:2 is novel and unobvious. There is actual reduction to practice of the disclosed species (see, e.g., Example 1). The specification indicates that the genus of variants of SEQ ID NO:2 does not have substantial variation since all of the variants be expressed at higher levels in metastatic cells relative to non-metastatic cells and must at least 95% identical to SEQ ID NO:2 or contain SEQ ID NO:2 with no more than 5 amino acid substitutions. The species disclosed, SEQ ID NO:2 (encoded for by SEQ ID NO:1), is representative of the genus because all members have substantial structural identity with SEQ ID NO:2 and because of the presence of an assay which applicant provided for identifying all of the variants of SEQ ID NO:2 that are expressed at higher levels in metastatic cells relative to non-metastatic cells. As indicated in the protein alignment of Figure 7 and as described, for example at page 6, line 28 of the specification, hsOAF has a high degree of similarity to Drosophila OAF. From the alignment shown in Figure 7, a skilled practitioner can readily identify which residues are conserved among the proteins and which can tolerate a conservative or non-conservative amino acid substitution, and predict which residues likely can be varied without losing function. Based on the alignment and on the provision of SEQ ID NO:1, the skilled artisan can also identify which nucleotides correspond to such conserved residues and predict which nucleotides likely can be varied without the encoded polypeptide losing function

Applicants further assert that claims 5 and 44 (and claims dependent therefrom) satisfy the written description requirement. Each of these claims recites a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO:2 with no more than 5 (claim 5) or not more than 3 conservative amino acid substitutions (claim 44). The protein of SEQ ID NO:2 is 273 amino acids in length. Thus, a protein with 5 amino acid substitutions is greater than 97% identical to SEQ ID NO:2. A protein with 5 amino acid substitutions is greater than 98% identical to SEQ ID NO:2. Accordingly, each of claims 5 and 44 is well within the hypothetical facts outlined in Example 14 of the Guidelines, facts the authors of the Guidelines explained are sufficient to meet the written description requirement.

New claims 45-47 depend from claims 5, 6 or 39 and recite, for example, that the encoded polypeptide comprises SEQ ID NO:10, that the encoded polypeptide comprises SEQ ID

NO:3, or that the nucleotides at positions corresponding to nucleotides 46-1173 of SEQ ID NO:1 are unchanged with respect to SEQ ID NO:1.

In view of the foregoing Applicants respectfully request the withdrawal of the written description rejection.

Enablement

Claims 1 and 5-11 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office alleges, *inter alia*, that Applicants' previously submitted "Declaration and the arguments are not commensurate in scope with the thrust of the rejection ... Applicants' specification has not provided enabling disclosure in which a definitive breast cancer diagnosis or implementation of the claimed polynucleotide, which has less than 100% sequence identity with the full length polynucleotide that encodes a variant sequence of SEQ ID NO:2 in assays." Applicants again respectfully disagree and submit that a skilled practitioner can practice the invention without undue experimentation (MPEP § 2164.01) because the specification is replete with guidance and working examples.

Preliminarily, as discussed above, the Office indicated that the rejection as it applied to claim 1 would be withdrawn upon entry of the previously filed amendment to claim 1. Applicants provide herein the amendment referred to by the Office. Accordingly, Applicants' comments are directed at pending claims 5-11 and new claims 36-47.

The pending claims are drawn to polynucleotides encoding polypeptides comprising an amino acid sequence that has a specified level of identity to SEQ ID NO:2 or a maximum number of conservative substitutions relative to SEQ ID NO:2, as well as homologs with a specified level of identity to polynucleotides encoding SEQ ID NO:2. In each claim, encoded polypeptides are expressed at a higher level in metastatic cells relative to non-metastatic cells.

The specification teaches how to prepare polynucleotides encoding polypeptides having at least 95% identity to SEQ ID NO:2 and also how to prepare polynucleotides having at least 95% identity to polynucleotides encoding SEQ ID NO:2. For example, the specification teaches how to prepare polypeptides that are functionally equivalent to hsOAF (see, e.g., page 11, lines

23-26; page 14, lines 10-15; and page 12, line 3, to page 14, line 15), e.g., by site-specific mutagenesis using PCR or oligonucleotides or synthetic chemical methods (page 15, lines 9-23). The specification also teaches how the degree of homology between proteins (see, e.g., page 11, line 27 to page 12, line 2) and polynucleotides (see, e.g., page 18, line 22 to page 19, line 2) can be calculated. Thus, the specification provides ample guidance for preparing the claimed polynucleotides and testing the encoded polypeptides for function. Accordingly, Applicants requests that the rejection of claims 5-11 be withdrawn. For at least these same reasons, Applicant submits that new claims 36-47 are also enabled. Applicant submits that these same teachings in the specification that provide an enabling disclosure for claims 5 and 11 (and their dependents) also enable one of ordinary skill in the art to make and use the polynucleotides of new claims 36-47.

The Office also alleges that there is no "enabling disclosure of which particular polynucleotides should be changed, mutated, deleted to bring forth a polypeptide with between one and ten conservative amino acid substitutions."

Claim 5 was amended to recite that there are "no more than 5 conservative substitutions to SEQ lD NO:2. As discussed above, the specification provides alignments identifying conserved portions of hsOAF, thereby providing guidance for production of variants that are expressed at higher levels in metastatic cells relative to non-metastatic cells. In addition, again as discussed above, the specification provides a means for determining whether a given polypeptide is expressed at higher levels in metastatic cells (e.g., Northern blot), procedures for making variants of SEQ ID NO:2, and describes assays which will identify variants of SEQ ID NO:2 that are likely to be phenotypically silent. Thus, the specification more than satisfies the enablement requirement particularly with respect to identifying which particular nucleotides could be "changed, mutated, [or] deleted."

The Office also appears to at least in part base the enablement rejection on an alleged lack of "experimental controls in the experimental design", referring to Example 2 which is said to lack a comparison with breast cells without disease. Applicants do not agree.

The enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under § 112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In applying the enablement requirement, the "invention" that must be enabled is that defined by the claims. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Pat. Off. Bd. App. 1987).

Applicants have provided evidence that the claimed polynucleotides, and polypeptides encoded by the polynucleotides, are differentially expressed in metastatic cancer tissue. The Office implies that a comparison to non-cancerous breast cells is required for enablement. The Office also raises a possibility that although "expression of SEQ ID NO:1 was increased in cell lines with high metastatic potential this does not rule out the expression possibly found in a normal control would not be the same as the expression found in low metastatic cell lines." Applicants respectfully assert that such a "possibility" is just a "possibility". Applicants invite the Office to supply specific evidence supporting this "possibility" or an affidavit under 37 C.F.R. 1.104(d)(2) if the information is based on the personal knowledge of the Examiner. Applicants remind the Office that "[w]ithout a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling." *In re Wright*, 27 U.S.P.Q.2d at 1513; *In re Marzocchi*, 169 U.S.P.Q. at 369.

Furthermore, it is noted that claims 5-11 and 36-47 recite polynucleotides encoding polypeptides related to SEQ ID NO:2, wherein the polypeptides are expressed at a higher level in ***metastatic*** cells relative to ***non-metastatic*** cells. As set forth in the specification (e.g., on page 32) expression of polypeptides was compared between ***metastatic*** cells (MDA-MB-231) and ***non-metastatic*** cell lines (MCF-7). There is no requirement for a comparison to non-cancerous breast cell lines.

The Office further alleges that "the experimental design presented in the specification continues to lack information regarding the applicability of mutants of polynucleotides and their corresponding encoded products which share limited sequence identity to SEQ ID NO:2 in

diagnostic methods relative to breast diseases." Applicants do not agree. Applicants respectfully assert that the specification supports using variants and homologs of hsOAF in diagnostic methods relative to breast disease. Furthermore, the specification supports the use of the claimed polynucleotides for such purposes as generation of antibodies, primers, probes and screens, as well as in therapeutic methods. Notwithstanding, Applicants remind the Office that enablement only need be shown for what is set forth in the claims. To sustain a rejection for lack of enablement, evidence would need to be provided showing that the claimed polynucleotides could not be made or used for **any** purpose without undue experimentation. No such evidence has been presented. The disclosure of the specification is more than sufficient to permit one to make and use the claimed polynucleotides.

The Office also alleges that "it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention." Applicants do not agree with the Office's conclusory statement. As discussed above, the specification does provide an enabling description of the claimed invention. Additionally, any experimentation that ***may*** be required of the skilled artisan would be nothing more than routine experimentation.

In re Wands concerned methods of using monoclonal antibodies for detecting hepatitis B surface antigen. Monoclonal antibodies of a particular antigenic specificity require a substantial amount of work to produce, and *Wands'* claims did not recite ***any*** sequence identity. Nonetheless, *Wands'* claims were held to be enabled. The present claims encompass polynucleotides which have a very high degree of identity to a reference sequence. The experimentation that would be required to produce the polynucleotides, if any, is well within the standard set for in *Wands*.

The key to analyzing an "undue experimentation attack" on the enablement of a patent, and therefore of an anticipatory reference, is in determining what is "undue," because some trial and error is permissible. See *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983) ("Assuming some experimentation were needed, a patent is not invalid because of a need for experimentation. A patent is invalid only when those skilled in

the art are required to engage in undue experimentation to practice the invention." (cite omitted) (emphasis in original)), cert. denied, 469 U.S. 851 (1984).

The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted).

The specification provides an enabling description of the claimed invention. The specification teaches a polynucleotide that is differentially expressed between high metastatic breast cancer cells and non-metastatic or low metastatic cancer cells, therefore relating to metastatic marker gene (see, e.g., page 6 lines 16-22). From the alignment shown in Figure 7, a skilled practitioner can readily identify which residues are conserved among the proteins and which can tolerate a conservative amino acid substitution, and predict which residues likely can be varied without losing function. The specification also notes that the invention "includes variations of the disclosed polypeptide which show comparable expression patterns or which include antigenic regions." (e.g., page 13, lines 16-21). Further, the specification teaches means that can be used to measure expression levels of hsOAF.

One of ordinary skill in the art would also know to ***avoid*** making non-conservative changes in areas of high homology as taught in Figure 7 and so would easily be able to generate variants of up to 95% sequence identity (or up to 5 amino acid substitutions) without undue experimentation. Producing variants with even higher sequence identity to SEQ ID NO:2 (at least 98%, for example) would take even less effort.

Should this rejection be maintained, the Office is asked to set forth reasons as to why it believes adequate enablement does not exist in the specification and in the knowledge of one of ordinary skill in the art and why, for example, one of skill in the art would be incapable of gleaning from the evidence in Figure 7 any clues as to where one could experiment with making 5 amino acid substitutions without necessarily destroying the activity of the protein. These

experiments would be simple and routine, given the disclosure in the specification. Thus, the specification is replete with guidance.

Notwithstanding the foregoing, Applicants also attach a declaration of Dr. Albert Lai. The declaration states that the specification provides sufficient guidance for a skilled artisan to practice the full scope of the claimed methods without undue experimentation.

Specifically, the declaration provides that the specification discloses the amino acid sequence of SEQ ID NO:2. The specification also discloses SEQ ID NO:1, which is a nucleotide sequence that encodes SEQ ID NO:2. The specification describes different types of sequence variations, such as variations that produce conservative amino acid substitutions (page 12, lines 3-11), truncations or deletions (page 12, lines 28-29), substitutions of charged residues with other charged residues (page 13, lines 22-23), site-directed mutants and mutants produced by alanine-scanning mutagenesis (page 14, lines 1 5). It notes that recombinant DNA methods may be used to produce polypeptides (page 15, lines 9-10). The specification provides an alignment of SEQ ID NO:2 with its Drosophila homologue and describes methods for determining the percent identity between two sequences (page 18, line 22- page 19, line 2). Given this information and knowledge and techniques routine in the art at the time the above-referenced application was filed, it would not require undue experimentation to make and use the claimed compositions and to practice the claimed methods. The specification provides ample guidance for producing and using, for example, a nucleic acid molecule that encodes a polypeptide of SEQ ID NO:2 having five or fewer conservative amino acid substitution, or a nucleic acid molecule that encodes a polypeptide at least 95% identical to SEQ ID NO:2.

The declaration also provides that nucleic acid variants have numerous uses, including but not limited to diagnostic uses. For example, the specification discloses that the claimed nucleic acid molecules can be used to express polypeptides, which in turn can be used as immunogens for the production of antibodies (page 17, line 5, to page 18, line 7; page 19, line 3, to page 21, line 10; and page 24, lines 1-7). Variant nucleic acid molecules can be used to express mutant polypeptides which are tested for biological activity such as receptor binding or proliferative activity (page 14, lines 5-6). The nucleic acid molecules are also useful for

production of probes or antisense reagents (page 22, lines 19-25; page 23, lines 1-20). These uses are not exclusive to nucleic acid molecules encoding sequences 100% identical to SEQ ID NO:2. Variant sequences are also applicable such uses.

In view of the foregoing Applicants respectfully request the withdrawal of the written description rejection.

Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

CONCLUSION

The foregoing represents a *bona fide* attempt to advance the present application to allowance. Applicants respectfully assert that all claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the undersigned attorney at (302) 778-8458 if such would expedite prosecution.

Please apply the fee for extension and any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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